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Short Communication

Opioid Receptors as Drug Targets for Newer Antidepressants

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Depression is a common, chronic, and potentially severe psychological condition characterized by sadness, loss of interest, and anhedonia. Depression alone accounts for about 4% of the global burden of disease and affects up to approximately 350 million people worldwide [1]. The current therapeutic agents of depression mostly target monoamine neurotransmission, inhibiting the reuptake of dopamine, serotonin, and norepinephrine. However, evidence suggests that other pathways beyond monoamines such as opioid signaling could regulate mood [2].

The three classic opioid receptors: *mu, delta*, and *kappa* interact with a family of endogenous opioid peptides known as β-endorphin, enkephalins and dynorphins, respectively. Ligands that activate *mu* or *delta* opioid receptors produce euphoria and pain relief, whereas ligands that activate *kappa* opioid receptor can produce opposite feelings [2]. The potent euphoric effects of known opiate drugs, and the high density of receptors in limbic brain areas, set the opioid system as a key player in mood control, and a potential target to treat emotional dysfunction [2].

Mu, kappa, or *delta* opioid receptor-targeted ligands have been explored as potential therapeutic candidates for major depressive disorder. Endogenous opioids and several selective opioid receptor ligands such as *mu* and *delta* opioid receptor agonists and *kappa* opioid receptor antagonists have shown promising data in animal models of depression [2]. However, some conflicting data exist in these preclinical studies where both depressant and antidepressant effects were reported by same ligands.

The fourth member of the receptor family is known as Nociceptin/Orphanin FQ peptide (NOP) receptor. NOP receptor and N/OFQ peptide are found in high concentration in human as well as rodent brain regions known to be involved in depression and drug abuse [3]. N/OFQ peptide is a 17 amino acid peptide which does not bind to *mu, delta*, or *kappa* opioid receptors. NOP receptors are coupled to $G_{i/o}$-protein and activation by N/OFQ peptide reduces cyclic AMP formation and blocks Ca^{++} channel. Therefore, activation of NOP receptors produces inhibitory effects causing reduction of release of neurotransmitters such as serotonin, norepinephrine, dopamine, etc [4]. The term nociception was coined for this receptor due to its involvement in pain pathway regulation. *In vivo* studies found that NOP receptors can modulate variety of other biological functions such as drug dependence, anxiety, depression, learning and memory, food intake etc [5-8].

Current neurochemical and clinical data indicate that N/OFQ peptide levels are increased during depression [9,10]. Hyperactivity of NOP receptor system is believed to send stress signals to hypothalamic pituitary adrenal axis to release stress hormones [11]. Accordingly, both peptide and non-peptide NOP receptor antagonists have attenuated depression-like behaviors in tests of antidepressant efficacy such as forced swim test and tail suspension test [12,13]. NOP receptor knockout mice has also demonstrated antidepressant-like phenotype relative to wildtype mice in the tests of antidepressant efficacy [14,15].

Overall, *delta, kappa* and NOP receptors are potential drug targets for newer antidepressants since they lack inherent abuse liability. Further preclinical studies on neurobiological effects and clinical studies on safety and efficacy are required to validate this new class of antidepressants.

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